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Self-Assessment of Color Categories and Its Relationship with HLA Profiling in Brazilian Bone Marrow Donors

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A B S T R A C T

The Brazil Ministry of Health maintains a Registry of Bone Marrow Donors that corresponds to approximately 12% of the Bone Marrow Donors Worldwide registry. This registry contains information on ethnicity (by self-assessment of color) and HLA-A, -B, and -DRB1 type. The self-assessment of color tool has been extensively used for admixed population characterization. In this context, Brazil represents a highly admixed population, resulting from 5 centuries of colonization and interbreeding, mainly, but not exclusively, among Native Americans, Europeans, and Africans. Here we evaluated self-assessed skin color and HLA genetic information from 71,291 bone marrow donors of southern Brazil to verify how likely is the HLA profiling correspondence within and between self-assessed color groups. We found that HLA itself was a better ancestry indicator than was self-assessed color. Therefore, self-assessment of color in highly admixed populations, such as that of Brazil, is not indicative of higher correspondence in the HLA profiles within skin color groups.

INTRODUCTION

The HLA system is very useful in population genetics studies, because HLA haplotypes and alleles are distributed at different frequencies in populations or ethnic groups around the world [1-3]. Therefore, it is expected that patients needing an allogeneic stem cell transplant are most likely to find their HLA-matched donor within their own population or ethnic group.

The Brazil Ministry of Health maintains a Registry of Bone Marrow Donors (REDOME) and a registry for people needing transplants (National Register of Bone Marrow Recipients). The information in these registries includes ethnicity (by self-assessment of color) and genetic typing of HLA-A, -B, and -DRB1 [4]. REDOME is part of the Bone Marrow Donors Worldwide registry, which has over 24 million donors as recorded by October 2014 [5]. As of June 2014 more than 3.2 million donors were registered in the REDOME registry [4], which correspond to approximately 12% of the Bone Marrow Donors Worldwide registry.

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The Brazilian population is highly admixed [6], resulting from 5 centuries of colonization and interbreeding, mainly, but not exclusively, among Native Americans, Europeans, and Africans [7]. This complex migration history has shaped the strong regional differences in the admixture proportions across the country. Southern Brazil, for instance, is characterized by a major European influence, even though Native American, Iberic, and African influences have also been important [8,9].

The self-assessment of color tool has been extensively used for Brazilian population characterization. The Instituto Brasileiro de Geografia e Estatística, which is responsible for the official census of Brazil, uses 5 pre-established, discontinuous color categories based on self-assessment: White, Brown, Black, Yellow, and Indigenous (Native American). In the last census (2010), the Instituto Brasileiro de Geografia e Estatística computed a population of 191 million Brazilians, presenting the following color percentages: 47.6% White, 43.1% Brown, 7.6% Black, .6% Yellow, 1.0% Indigenous, and .1% with no declaration [10]. These color categories are used as proxies for ancestry, and even though they may be based on a complex phenotypic evaluation, skin pigmentation is the most relevant character [11]. The use of this term rather than the term "race" is justified, because it captures the continuous aspect of phenotypes [12]. "Brown" may express the general admixed character of 1 individual, rather than referring specifically to intermediates between Whites and Blacks [13]. The term "Yellow" refers to those individuals exhibiting an East Asian phenotype.

Here we analyzed self-assessed skin color and HLA genetic information from bone marrow donors in the state of Rio Grande do Sul, Brazil to verify how likely is the HLA profiling correspondence within and between self-assessed color groups in a highly admixed population.

METHODS

Sample

In the present study, we used the HLA data of 71,291 bone marrow donors from the state of Rio Grande do Sul, Brazil, which represents 7.9% of all Brazilian donors. HLA typing was performed at the Laboratory of Immunology of the Hospital de Clínicas de Porto Alegre from January 2008 to October 2012. The available information included gender, town of residence, ethnic group, and genotyping at a low resolution (allelic group) for the HLA-A, -B, and -DRB1 loci (Luminex LABType SSO system; One Lambda, Inc., Canoga Park, CA). The ethnic group was informed by the donor's own perception based on skin color.

As parental populations, we used data from European (Portugal, Italy, Germany, and Spain), African (Guinea Bissau, Cape Verde, Sao Tome, and Rwanda), and Native American (Uro from Peru; Zapotec, Mixteco, Mazateca, Mixe, and Huasteca from Mexico; Mayan from Guatemala) populations. Data on all these parental populations are available in the Allele Frequencies database [14]. This study was approved by the ethics committee of the Grupo de Pesquisa e Pós-Graduação do Hospital de Clínicas de Porto Alegre under the number 386.216.

Statistical Analysis

Arlequin 3.5 software [15] was used to estimate allele and haplotype frequencies, for testing of the Hardy-Weinberg equilibrium, and for computing the Reynolds genetic distances between populations. Haplotypes were estimated using the maximum likelihood algorithm. The various self-assessed color groups of the Rio Grande do Sul population were compared with those of the respective parental populations by computing the Reynolds' genetic distances, based on the HLA-A, -B, and -DRB1 allelic frequencies, which were taken independently. The mean genetic distances computed for the 3 loci were plotted using a multidimensional scaling analysis with XLSTAT 2014.3.07 software (Addinsoft, Inc., Brooklyn, NY).

To verify whether the HLA distribution and compatibility are consistent within and between groups self-assessed as Black and White, pairwise comparisons were performed using Cervus 3.0.7 software [16], using as matching criteria 6/6 alleles at low resolution level for HLA-A, -B, and -DRB1 genes. The matching rate was calculated in Winpepi 11.43 [17], and the odds ratio and chi-square were calculated using IBM SPSS, Version 20.0 (IBM Corp., Armonk, NY).

RESULTS AND DISCUSSION

Regarding self-assessed color, most people in the sample were classified as Whites (93.7%, n = 66,830), followed by Blacks (5.5%, n = 3,897) and Browns (.7%, n = 472). Only 76 individuals declared themselves as Yellow (.08%) and even fewer (.02%, n = 16) as Indigenous.

There was no statistically significant differences between the observed and the expected heterozygosities at any locus (HLA-A: observed, .870; expected, .874; HLA-B: observed, .927; expected, .932; HLA-DRB: observed, .895; expected, .896). The estimated allele frequencies for HLA-A, -B, and-DRB1 for the entire data set and in each ethnic group are shown in Supplemental Table 1. There was considerable variation in the allele frequencies across ethnic groups. HLA-A*30 was 8.6% in Blacks, 6.2% in Browns, and 3.2% in Whites. Consistent with these observations, HLA-A*30 is found at higher frequency in African populations (29% in Cameroon

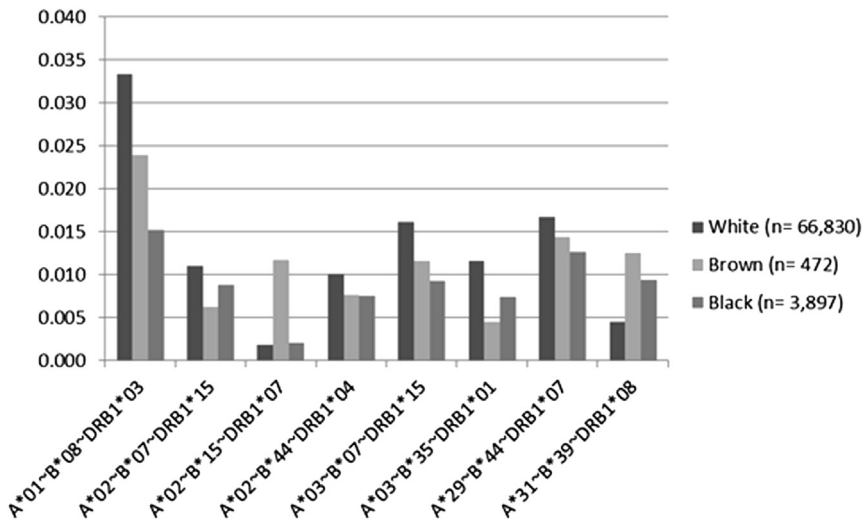

Figure 1. Frequencies of HLA-A, -B, and -DRB1 haplotypes in each ethnic group. Only haplotypes with frequency ≥ 1% in at least 1 ethnic group are listed.

and 23% in Mozambique) [18,19] but not in European populations [20,21].

The typically Caucasian A*01∼B*08∼DRB1*03 haplotype was the most frequent (3.2%), being most common in our sample among Whites (3.3%), followed by Browns (2.4%), Blacks (1.5%), and Yellows (.7%) (Figure 1). The A*03∼B*07∼DRB1*15 and A*29∼B*44∼DRB1*07 haplotypes were also more frequent in Whites (1.6% each) than in Browns (1.1% and 1.4%, respectively) and Blacks (.9% and 1.2%, respectively).

Interestingly, the A*02∼B*15∼DRB1*07 haplotype showed a frequency of 1.2% in Browns but only .2% in either Whites or Blacks. This haplotype is found at low frequency only in European and North American populations [14] but has a 1.3% frequency in the Azores [22]. The state of Rio Grande do Sul experienced a strong Azorean immigration during the 18th century. Between 1752 and 1754, approximately 500 couples originating from the Azores archipelago arrived in Porto Alegre, the largest city in Rio Grande do Sul [23], and by 1780 half of Porto Alegre's population was Azorean or of Azorean descent [24]. Uniparental genetic markers, as well as the typically Azorean SCA3 mutation, are frequent in the Rio Grande do Sul population [9,25].

The A*31∼B*39∼DRB1*08 haplotype also appears more frequently in Browns (1.3%) than in Blacks (.9%) and Whites (.4%). This haplotype is not represented in the parental populations investigated, but it has already been observed in another Brazilian population (.5% in Ribeirão Preto, São Paulo state) [26]. Indeed, the existence of new haplotypes is expected in admixed populations. Notably, the 2 haplotypes mentioned above are more frequent in the Brown color group, which refers to individuals resulting from mixes between Africans and Europeans, Africans and Indigenous, Europeans and Indigenous, or even from a blend of all parental groups over time [13,27].

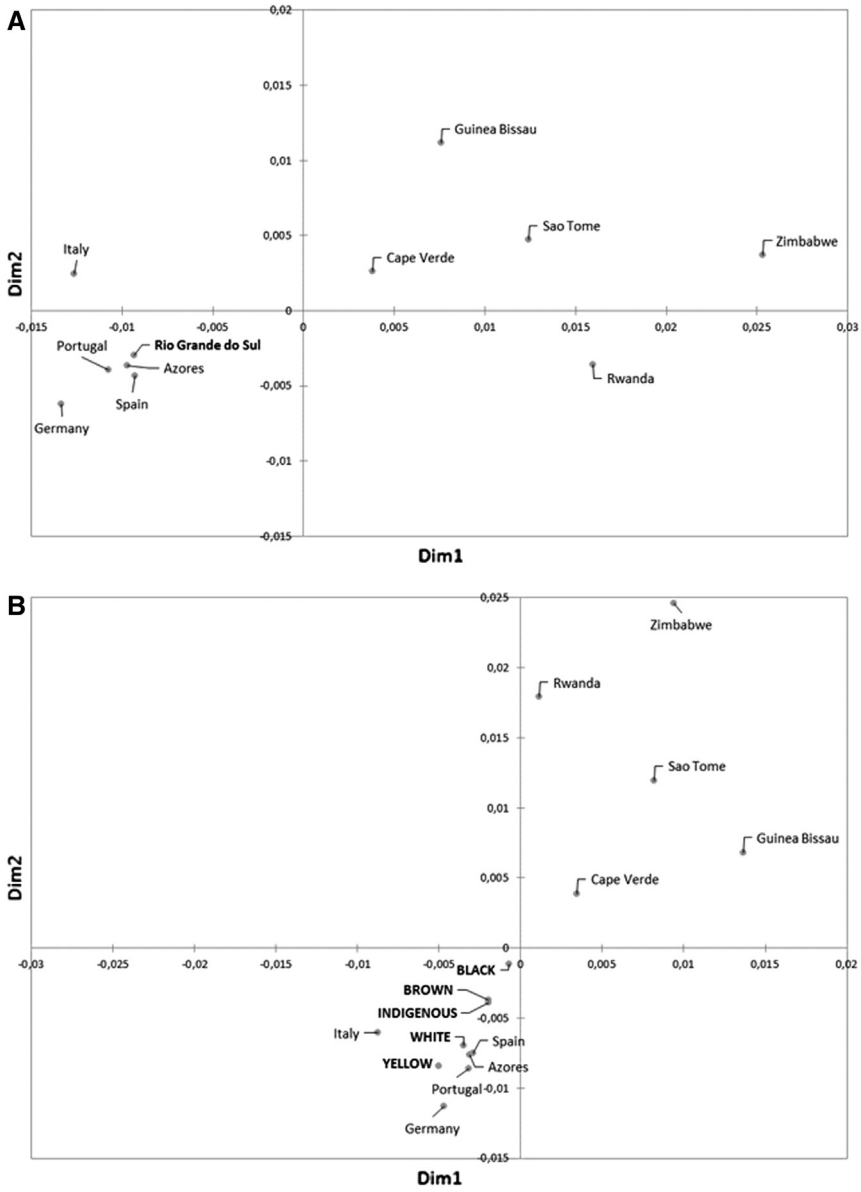

Figure 2. Multidimensional scale based on mean Reynolds' genetic distance calculated for HLA-A, -B, and -DRB1 loci. (A) Rio Grande do Sul, European, and African populations (stress value = .143). (B) Ethnic groups of Rio Grande do Sul, European, and African populations (stress value = .173).

Table 1
HLA Matches Within and between Ethnic Groups (Self-Assessed Color Categories)

Ethnic Group	No. of Matches	Match Rate (95% CI)	Odds Ratio (95% CI)
Black (n = 3897)	95	1.25E-05 (9.98×10^{-6}-1.51×10^{-5})	.879 (.717-1.078)
White (n = 66,830)	68,986	3.09E-05 (3.07×10^{-5}-3.11×10^{-5})	2.169* (2.098-2.241)
Between Black and White	3709	1.43E-05 (1.39×10^{-5}-1.46×10^{-5})	1

* $P < 1E-05$ (chi-square test).

The present sample of the Rio Grande do Sul population was most similar to the populations of Spain and Portugal, followed by those of Italy and Germany (Figure 2A), which agrees with the historical data on the initial settlement of southern Brazil. The largest parental contributions came from these 4 aforementioned countries, either through direct immigration from Europe or because of the proximity to the borders of Hispanic countries, such as Argentina and Uruguay. Rio Grande do Sul itself was part of the Hispanic colonization from the 16th to 17th centuries [23]. Guerreiro-Junior et al. [9] found similar results when studying uniparental genetic markers, particularly mitochondrial ones, in Rio Grande do Sul's self-reported white population.

When the self-assessment of color alone was considered, Brown and Indigenous individuals overlap on the graph, intermediate between Blacks and Whites (Figure 2B). This result may lead to the confusion of the perception of ancestry with that of skin color, because both Brown and Indigenous tend to be intermediate skin color phenotypes, between Blacks and Whites. Although individuals self-assessed as Blacks are distant from Whites on the graph, they remain much closer to European populations genetically than to the African parental populations. An explanation is the absence of the parental Bantu groups in this comparison. Bantu speakers represent the majority of the slaves that were brought to Brazil between the 15th and 18th centuries [8].

Our results regarding the matching probability within the self-assessed as Black group was 1.25×10^{-5} (odds ratio, .879), whereas in the self-assessed as White group it was 3.09×10^{-5} (odds ratio, 2.169), almost 2.5 times higher (Table 1). When we tested the matching rate between groups, the result was similar to that found in the self-assessed as Black group (1.43×10^{-5}). Considering this, we could infer the self-assessment of color is not a differential predictor to find higher HLA correspondence in the same color group, at least in highly admixed populations, as is the case in Brazil. The higher probability of finding an HLA correspondence within the White group compared with the Black group could be explained by the fact that, considering the HLA system, white populations are less polymorphic than African-American populations [28], which could favor the increased frequency of haplotypes typically see in whites, as can be observed in Table 1.

Lins et al. [11] showed a disparity between the self-assessed and genetic ancestries of the admixed Brazilian populations. Recently, a study of 1594 individuals from Brazil observed that individuals self-assessed as Blacks had around 40% of European genetic ancestry, whereas those self-assessed as mestizos (Brown or "Pardo") had around 70% of European genetic ancestry [29]. Other studies with ancestry-informative markers on different populations in Brazil have also shown a discrepancy between self-declared information and genetic ancestry [30-33].

Because HLA alleles and haplotypes occur at different frequencies among the different ethnic groups, an HLA match between a donor and a recipient is more likely if they share the same ethnicity or ancestry. In the United States, the National Marrow Donor Program uses a system that takes self-declared ethnicity into account when predicting the likelihood of an HLA match [34]. In cord blood allogeneic transplants, better HLA matching was observed when the patient and the cell source were of matching ethnicity [35]. However, the ancestry of the matched donor does not appear to affect the outcome of hematopoietic stem cell transplants [36], although further studies are needed to confirm these data. Furthermore, it has been shown that patients from ethnic minority groups have a lower chance of finding a match, and this is not simply because of the smaller number of donors from these minorities. African-Americans, for example, are more polymorphic with respect to HLA types and are hence less likely to find donors in registries of any given size [28].

In our study, the HLA type itself was a better ancestry indicator than the self-assessment of color. Therefore, the self-assessment of color in highly admixed populations, such as that of Brazil, is not indicative of higher correspondence in the HLA profiles within skin color groups.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.bbmt.2015.02.019

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